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Oral and Periodontal Diseases in Consanguineous Marriages

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Abstract

Periodontitis is defined as an inflammatory disease of supporting tissues of teeth characterized by progressive destruction of the periodontal ligament and alveolar bone. Periodontal manifestations of these genetic disorders or syndromes, such as familial and cyclic neutropenias, granulomatous disease, agranulocytosis, Langerhans' cell disease, glycogen storage disease, hypophosphatasia, leucocyte adhesion deficiency, and Papillon-Lefèvre, Chédiak-Higashi, Cohen, Ehlers-Danlos, Marfan, Down, Haim-Munk, and Kindlers syndromes, imitate some types of periodontal diseases. Most of these syndromes have autosomal-recessive characterization and can be seen commonly in consanguineous marriages. Therefore, consanguineous marriages have generally been accepted as having important detrimental effects on offspring. There is a lot of genetic research about consanguineous marriage and its detrimental effects on offspring. Although consanguineous marriages are common in the world, the relationship with oral and periodontal diseases has not been thoroughly investigated. We do not have enough of an understanding of the effects of consanguineous marriage on oral and periodontal diseases. In this chapter, previous studies in the literature related to this subject will be investigated and evaluated, and then this research will be related to oral and periodontal diseases. Therefore, this chapter will guide further research. The aim of this chapter is to show the relation between consanguineous marriages and oral-periodontal diseases.

Keywords: periodontal diseases, genetic disorders related with periodontitis, consanguinity

1. Introduction

1.1. Oral and periodontal health

Etymologically, the word “health” was reproduced from the Old English “hale” and means wholesome, sound, or well-being [1]. Although there is significant improvement in oral health in developed countries, oral disease still persists as a global problem, especially among underprivileged groups in both developing and developed countries [2]. The global public health problems associated with oral disease are a serious burden on governments [3]. In the Preamble to the Constitution of the World Health Organization (WHO) [4, 5], health was described as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” Moreover, the Preamble proposes: “The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.” Therefore, the WHO suggests that complete health should be an endpoint that people and society should struggle to achieve. At the Ottawa Charter for Health Promotion (1986), the WHO added that “health is a resource for everyday life, not the objective of living.” This means that health is a necessity for people’s daily lives. “Health promotion is the process of enabling people to increase control over, and to improve, their health.” For this purpose, government and health care workers have important duties to extend health services for people. What is “complete physical and mental health” and “absence of disease or infirmity”? Unfortunately, these questions have not been—and probably never will be—answered satisfactorily [1].

Tooth caries, periodontal diseases, loss of teeth, oral mucosal lesions, and cancers are some of the major oral health problems that the public face. Pain and trouble with eating, chewing, smiling, speaking, and communication due to discolored, rotten, or missing teeth are factors that adversely affect people’s everyday lives [6]. Periodontal diseases have historically been considered one of the most important global oral health burdens for governments [7, 8].

Periodontal health means the absence of any clinical signs and symptoms of current or past periodontal disease [1]. For many patients, healthy periodontium is comfortable and free of functional and aesthetic problems [9]. The American Academy of Periodontology (AAP) has defined health as “the condition of a patient when there is function without evidence of disease or abnormality” (AAP 2001). It could be said one has periodontal health if there are no disease signs and symptoms of periodontal tissues. The diagnosis of periodontal disease is usually documented by the presence of bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment level (CAL) loss. However, other symptoms of periodontal disease include the results of chronic gingival inflammation and the destruction of tooth-supporting tissues, such as redness, bleeding on brushing, loosening of affected teeth, and persistent bad breath [10]. These symptoms affect the quality of daily life of people.

2. Classification system for periodontal diseases and conditions

The most commonly accepted systems of classification of periodontal disease have been offered by the American Academy of Periodontology (AAP). (*International Workshop for Classification of Periodontal Diseases in 1999*) [11].

Partial list of periodontal disease which may be associated with genetic conditions has been given below [11].

(1) **Gingival lesions of genetic origin**

- (a) Hereditary gingival fibromatosis
- (b) Other

(2) **Chronic periodontitis**

- (a) Localized chronic periodontitis
- (b) Generalized chronic periodontitis

(3) **Aggressive periodontitis**

- (a) Localized aggressive periodontitis
- (b) Generalized aggressive periodontitis

(4) **Periodontitis as a manifestation of systemic diseases**

(a) **Associated with hematologic disorders**

- Acquired neutropenia
- Leukemias
- Other

(b) **Associated with genetic disorders**

- Familial and cyclic neutropenia
- Down's syndrome
- Leukocyte adhesion deficiency syndromes
- Papillon-Lefèvre syndrome
- Chediak-Higashi syndrome

- Langerhans cell disease (histiocytosis syndromes)
- Glycogen storage disease
- Chronic granulomatous disease
- Infantile genetic agranulocytosis
- Cohen syndrome
- Ehlers-Danlos syndrome (types IV and VIII)
- Hypophosphatasia
- Crohn disease (inflammatory bowel disease)
- Marfan syndrome
- Other

(c) **Not otherwise specified (NOS)**

2.1. Periodontitis

Periodontal diseases are major global oral health problems that occur on teeth and tissues around the teeth. One of the most common periodontal disease is periodontitis. Periodontitis starts first on gingiva and progresses to periodontal ligament and alveolar bone, which causes the degradation of supporting tissues of teeth and eventually leads to loss of teeth [12]. Periodontitis is primarily caused by pathogenic microorganisms in the biofilm. The other predisposing factors are genetic and environmental factors [13].

The shifting of the nucleotides in the genes can lead to periodontitis. Susceptibility to periodontitis among patients is different [14]. The correlation between genetic composition and periodontal diseases is complex and not clearly explained [11]. Only a special gene is not correlated with the all mechanisms of the disease [14]. Family history is a criterion for periodontal diseases that must be taken into consideration [11]. Although the family aggregation may be affected by both genetic and environmental factors, studies on twins reared apart have shown that genetic factors are effective parameters for diseases [15].

According to the studies on monozygotic and dizygotic twins, 50% of variance in periodontal disease has been associated with genetic factors [16]. Also, genetic factors have an important role on the balance between protective and destructive chemical mediators [17, 18]. Genetic components may determine the roles of the immune system, host response, and cytokines in periodontal disease [19]. Researchers who have investigated the genetic effect on periodontal diseases have focused on familial aggregation and genetic components of aggressive periodontitis (AP) [20], periodontitis associated with Mendelian-inherited diseases [20], twin research [15, 21], and segregation analysis and linkage studies [22, 23].

2.1.1. Genetic studies on chronic periodontitis and aggressive periodontitis

Chronic periodontitis (CP) is the most common type of periodontitis and shows a slow rate of progression. It can begin in adolescence but usually does not become clinically significant until 35 years of age [24, 25]. There is no proven genetic determinant for patients with chronic periodontitis in any research. To determine the role of genetic factors in chronic periodontitis, twin and family studies are the optimal methods [26].

In a study, chronic periodontitis was shown to be 50% of heritable [16]. Chronic periodontitis has shown familial heredity in a Dutch population epidemiological study [27]. Also, there is some evidence that shows a correlation between IL-1, IL-6, IL-10, VDR, and CD14 genes and chronic periodontitis susceptibility [26]. IL-1 polymorphisms have been associated with severity of periodontitis [28, 29].

Aggressive periodontitis (AP) is a type of periodontitis that is characterized by destruction of periodontal tissues and alveolar bone, despite the presence of a small amount of dental plaque. It occurs in systemically healthy individuals who are generally younger in age, but patients may be older [11]. There are two types of aggressive periodontitis. Generalized and localized forms of aggressive periodontitis are rare types of periodontal disease that first occur with rapid attachment and bone loss and tend to appear in the families [30]. The prevalence of localized aggressive periodontitis (LAP) is less than 1% and that of generalized aggressive periodontitis (GAP) is 0.13%. Black populations are at higher risk than whites; male population is at higher risk of GAP than females [31].

Both genetic and environmental factors have crucial roles in the occurrence of these diseases. Chronic periodontitis and aggressive periodontitis are also affected by the combined effects of environmental and genetic factors [32, 33].

Although the familial aggregation of aggressive periodontitis is known, the mode of inheritance is still unclear. Family linkage studies have informed different modes of inheritance such as X-linked-dominant [34], autosomal-dominant [23], autosomal-recessive [22], or both X-linked-dominant and autosomal-dominant [35].

Polymorphisms in the cytokine genes, such as interleukin-1 receptor antagonist (*IL-1RN*) and interleukin-4 (*IL-4*), have been found to be positively correlated with aggressive periodontitis [36, 37]. A combination of two alleles of interleukin, *IL-1A*⁻⁸⁸⁹ and *IL-1B*⁺³⁹⁵⁴, have been found associated with aggressive periodontitis [38–40]. *IL-4*-590 T/T, *IL-4*-34 T/T genotype, *IL-6*-174G allele, and *IL-6*-572 C/G polymorphism are associated with aggressive periodontitis [41, 42]. A relationship between *IL-6*-1363,-1480 polymorphism and LAP susceptibility has been found [43].

IL-10 promoter polymorphisms at positions -1082 G-A, -819C-T, and -590C-A [44] and FPR348 T-C gene polymorphism in African-American people [45] are potential risk indicators for GAP. It is said that Fc gamma RIIIb-NA2 allele and Fc gamma RIIIb-NA2/NA2 genotype, composite genotype Fc gamma RIIIb-NA2/NA2, FCgammaRIIIa-H/H131 [46], and FCgamma polymorphisms [47] may lead to aggressive periodontitis. IL-1 (*IL-1α* and *IL-1β*) genes genotype-positive

individuals have higher levels of virulent bacterial complexes. The number of virulent bacterial species in deep pockets is seen at higher levels in IL-1 genes genotype-positive people than genotype-negative people [48].

Angiotensinogen, cathepsin C, E-selectin, formyl peptide receptor, NADPH oxidase, plasminogen activator inhibitor 1, calprotectin, tissue inhibitor of matrix metalloproteinase 2, and tissue plasminogen activator have been correlated with aggressive periodontitis [49]. TLR-4 399 Ile polymorphism has shown a protective effect against aggressive periodontitis in contrast to chronic periodontitis [50]. HLA-DR4 gene polymorphism is found in higher frequency in rapidly progressive periodontitis patients, and HLA-A9, B-15 gene polymorphisms are found to be significantly elevated [51, 52]. HLA-DQB1 plays a crucial role in pathogenesis of aggressive periodontitis [53].

2.1.2. *Role of genetic factors in periodontitis as a manifestation of systemic diseases*

Periodontal diseases include a wider spectrum of diseases than just periodontitis. Some periodontal diseases are affected by genetic variations. Thus, it could be said that genetic factors play a crucial role in periodontal health and disease (**Table 1**) [16, 54].

Syndrome	Mutated gene	Chromosome region
Ehlers-Danlos syndrome	Collagen alpha-1(V) gene (COL5A1) or the collagen alpha-2(V) gene (COL5A2) Type III collagen for EDS type IV, unknown for EDS type VIII	9q34, 2q31
Papillon-Lefèvre syndrome and Haim-Munk syndrome	Cathepsin C (CTSC gene) (dipeptidyl aminopeptidase)	11q14.1–q14.3
Hypophosphatasia	ALPL, tissue non-specific alkaline phosphatase	1p36.12
Chediak-Higashi syndrome	Lysosomal trafficking regulator CHS1/LYST, abnormal transport of vesicles to and from neutrophil lysozyme caused by mutations in lysosomal trafficking regulator gene (LYST)	1q42.1–q42.2
Leukocyte adhesion deficiency type I	Beta-2 integrin chain	21q22.3
Leukocyte adhesion deficiency type II	GDP-fucose transporter-1	11p11.2
Congenital and cyclic neutropenia	ELANE	19p13.3
Glycogen storage disease	SLC37A4	11q23.3
Down syndrome	Multiple, vertical trisomic regions at least 5Mb (megabase) long	Trisomy 21

Table 1. Some syndromes with clinical manifestations of severe periodontitis.

3. Consanguineous marriages

Linguistically, the word “consanguinity” is reproduced from two Latin words: “con” meaning common or shared and “sanguineus” meaning blood. The meaning of consanguineous marriage is a relationship between biologically related individuals. As a clinical genetic term, “a consanguineous marriage” is a union between couples who are related as second cousins or closer [55–57]. The terms of inbreeding and consanguinity are used to define relations between couples who have at least one common ancestor [58, 59]. It is estimated that more than one billion of the global population who live in different communities and countries prefer consanguineous marriage [56, 60]. At present, this rate corresponds about 20% of world populations [56]. Categories of consanguineous marriages are different (**Figure 1**).

Consanguinity rates differ in communities depending on religion, culture, and geography. The prevalence is high among Middle Eastern and Arab citizens [61]. The highest rates of consanguineous marriages in the world are seen in many Arab countries where 20–50% of all marriages include consanguineous marriages, especially first cousin marriages [62]. In developed countries, the rate of consanguineous marriage has decreased to a low level but includes different ethnic groups, some of which continue to practice their traditional cultural habits [63]. It is commonly accepted that consanguinity is more prevalent among underprivileged persons in poor communities [64–66]. Education level and socio-economic status of the persons may have a potential effect on consanguinity [67].

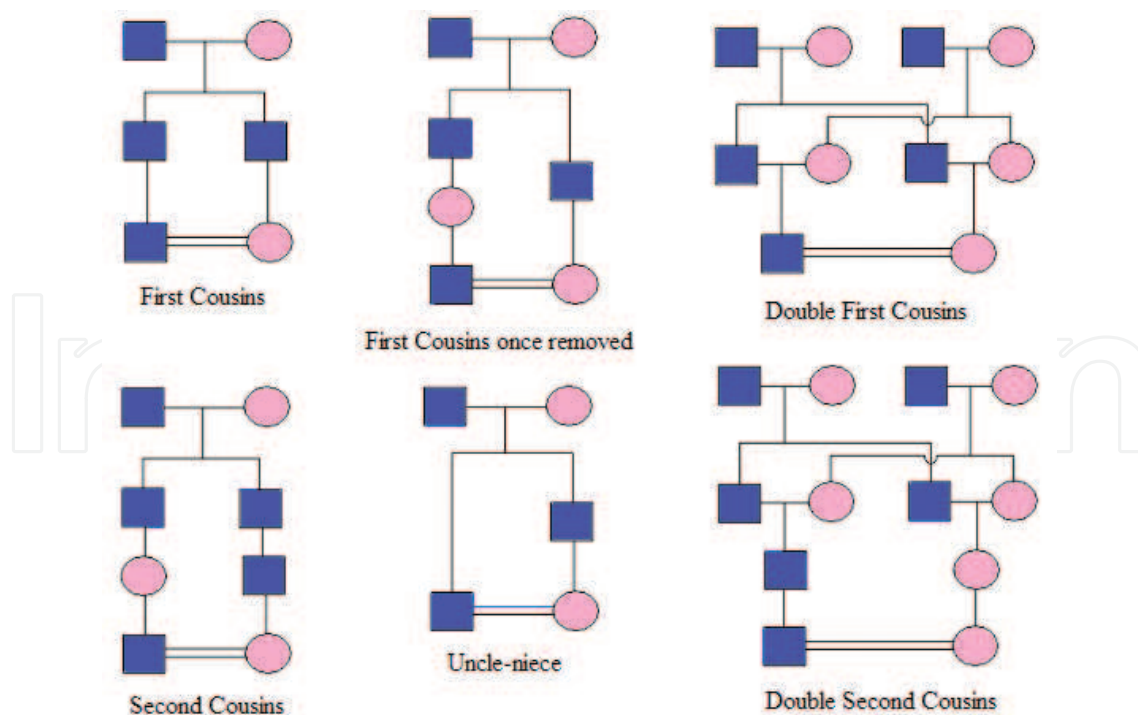


Figure 1. Categories of consanguineous marriages.

Studies of consanguineous marriage and genetic disorders have yielded conflicting results [68, 69]. The correlation between relationship and proportion of genes is as follows [70] (**Table 2**).

Research on the association between consanguinity and the different parameters of oral and periodontal health is limited, both in quantity and in quality [71].

Consanguineous marriage leads to increased genetic homogeneity of inbred individuals. Inbred individuals have similar paternal and maternal genetic materials. The detrimental effects of inbreeding are the result of homozygosity of harmful genes [58].

Consanguineous marriages have generally been accepted as having important detrimental effects on offspring [72, 73]. Some of the rare autosomal-recessive diseases can commonly be seen in consanguineous marriages. Health workers should be aware of these conditions and should inform patients about possible syndromes [73, 74].

The high consanguinity rates in communities could induce the expression of autosomal-recessive diseases. These include very rare or new syndromes. Therefore, health workers must be aware of the risks associated with consanguineous marriages. Currently, many young consanguineous couples planning to have children are afraid of the consequences of consanguinity for their offspring [74].

If there is a closer biological relationship between parents, identical copies of one or more detrimental recessive gene will be transferred to their offspring [73]. If one of the parents is affected, in general, consanguineous marriage does not increase the risk for autosomal-dominant conditions in offspring [75].

If parents are not related, their offspring have a 2–3% possibility of inheriting detrimental genes. If parents are first cousins, their offspring have up to 5–6% possibility of inheriting detrimental genes because they will both transport the same autosomal-recessive mutation. If parents are consanguineous, no increased rate is observed for X-linked or autosomal-dominant genes [70].

Although consanguineous marriages are common in the world, the effects on oral diseases have not been thoroughly investigated. We do not have enough of an understanding of the effects of consanguineous marriage on oral and periodontal diseases.

Relationship	Relationship degree	Proportion of genes
Identical (monozygotic) twins		100%
Brothers and sisters, non-identical (dizygotic) twins, parents and children	First degree (1°)	½, 50%
Uncles and aunts, nephews and nieces, grandparents and half-brothers and half-sisters	Second degree (2°)	¼, 25%
First cousins, half-uncles and aunts and half-nephews and nieces	Third degree (3°)	1/8, 12.5%

Table 2. Proportion of genes among the relatives [70].

4. Genetic disorders with periodontal manifestations and consanguinity

Genetic disorders with periodontal manifestations are as follows: familial and cyclic neutropenias (CyN); Crohn disease; chronic granulomatous disease (CGD); agranulocytosis; Langerhans' cell disease; glycogen storage disease; hypophosphatasia; and leucocyte adhesion deficiency, Papillon-Lefèvre, Chédiak-Higashi, Cohen, Ehlers-Danlos (types 4 and 8), Marfan, Down, Haim-Munk, and Kindlers syndromes [13].

Familial gingival fibromatosis is a rare hereditary condition that causes aesthetic, functional, psychological, and masticatory problems for patients [76]. It may manifest as an autosomal-dominant and autosomal-recessive mode of inheritance [77, 78]. Consanguinity has been observed in the recessive mode of familial gingival fibromatosis [79, 80].

Leukocyte adhesion deficiency (LAD) type I is caused by the combined loss of expression on the surface of leukocytes of the leukocyte integrins LFA-1, Mac-1, and p150, 95. It is a rare, inherited, autosomal-recessive, immunodeficiency disease [81]. Leukocyte adhesion deficiency type II is a disease with impaired fucosylation leading to an abnormal sialyl-lewis X (CD15). It is characterized by recurrent infections, persistent leukocytosis, and severe mental and growth retardation [82]. Leukocyte adhesion deficiency II was first described in two nonrelated children who have consanguineous parents [83, 84]. In a study, consanguinity has been found as a major factor for the distribution of LAD [85].

Langerhans-cell histiocytosis (LCH), once known as histiocytosis X, is considered a rare and non-hereditary disorder that includes a variety of diseases characterized by the dysregulated proliferation of Langerhans cells and infiltration of organs by pathological Langerhans cells [86]. Research on the relationship between periodontitis and consanguineous marriage is limited [87].

Glycogen storage disease type 1 (GSD-1) is a autosomal-recessive disorder that is caused by a deficiency in microsomal glucose-6-phosphatase activity [88]. Because of neutrophil dysfunction and neutropenia, there is an increased susceptibility to bacterial infection. This leads to symptoms of periodontitis [89, 90]. In a linkage analysis, consanguineous marriages and glycogen storage disease type 1 have been found to be related to each other [88].

Chronic granulomatous disease (CGD) is a rare inherited disease of the innate immune system that is characterized by impaired phagocyte microbicidal activity. It is caused by genetic defects in the superoxide-generating NADPH oxidase of phagocytes [91]. In a retrospective study, 14 patients with CGD were investigated. According to results of this study, a high consanguinity rate (75%) was observed [92].

Infantile genetic agranulocytosis is rare, inherited as an autosomal-recessive pattern, and characterized by severe neutropenia [93]. Patients may suffer from recurrent gingivitis and even severe periodontitis [94]. To have a family history of consanguineous parenthood may be a predisposing factor for infantile genetic agranulocytosis [95].

Some rare syndromes affecting phagocytes, epithelia, connective tissue, and teeth may cause severe periodontal conditions. Some genes that were responsible for these syndromes were identified. Haim-Munk and Papillon-Lefèvre syndromes (PLS) are rare autosomal-recessive

disorders associated with periodontitis onset at early stage of the life. At childhood, both deciduous and permanent teeth are lost early. Mutations in the cathepsin gene (CTSC) on chromosome 11q 14–21 are the cause of PLS [96–98]. Papillon-Lefèvre syndrome is an autosomal-recessive disorder, and consanguinity in 20–40% of patients has been demonstrated in some studies [99, 100]. Consanguineously married parents may have offspring with PLS [101, 102]. In patients with PLS, deciduous teeth are lost early, but gingiva remains healthy. When permanent teeth erupt, gingivitis and periodontitis occur and all permanent teeth except the third molars are lost in a short time [103].

Ehler-Danlos syndrome is a group of autosomal-recessive disorders that affect the connective tissues such as skin, blood vessels, joints, etc. [104, 105]. In a case study, a patient with third-degree consanguineous parents has been described as having the appearance of old age, hypermobile joints, and skin laxity [106].

Once a patient's host response or immune system is impaired, severe periodontal disease and loss of periodontal tissues are often seen. Various systemic diseases such as leukemia, thrombocytopenia, and leucocyte disorders, such as agranulocytosis, cyclic neutropenia, and leucocyte adhesion deficiency, could result in increased severity of periodontal disease [13].

Cyclic neutropenia (CyN) is defined as an absolute neutrophil count (ANC) less than $0.5 \times 10^9/L$ for at least 3–5 days per approximately 21-day cycles [107]. Neutrophil elastase (NE) gene (ELANE, formerly known as ELA2) located on chromosome 19p13.3 is the suspected gene that is the only known genetic defect in patients with CyN. This condition shows an autosomal-dominant transmission [108, 109]. Alangari et al. [110] have investigated both cyclic neutropenia and severe congenital neutropenia (SCN) phenotypes in an extended consanguineous multiplex family. According to results of this study, they have shown for the first time that a G6PC3 homozygous mutation resulted in a phenotype that is compatible with CyN in addition to the classical phenotype of SCN. They have reported that mutations in that gene could be said to have an autosomal-recessive pattern of inheritance in patients with CyN.

Chediak-Higashi syndrome (CHS) is a severe autosomal-recessive disease. It is characterized by partial oculocutaneous albinism, a predisposition to infections, the presence of abnormally large granules in many different cell types, and insufficient natural killer cell activity [111–113]. In consanguineous families, patients with Chediak-Higashi syndrome were found to have homozygous for the haplotype defined by the markers D1S235 and D1S2649 [111].

Cohen syndrome is a rare autosomal-recessive syndrome [114]. Diagnosis of Cohen syndrome is determined as the presence of at least seven of the following clinical symptoms as originally reported by Cohen et al. [114] and further described by Norio et al. [115]: mental retardation, microcephaly, characteristic facial appearance, slim tapering extremities with relative truncal obesity, hypotonia, joint hyperextensibility, benign neutropenia, and ophthalmic abnormalities such as myopia and retinal dystrophy. Cohen syndrome has been shown to be related with consanguinity [116].

Down syndrome is one of the most common human chromosomal disorders. Incidence of Down syndrome is quite high about 1 in 700 live births [117]. It is a result of an extra copy of the human chromosome 21 (trisomy 21) [118], and it is the most frequent genetic cause of

mental retardation [117]. Studies investigating the relationship between Down syndrome and consanguineous marriage are contradictory [119–121].

Marfan syndrome is an autosomal-dominant disorder and a heritable disorder of fibrous connective tissue. The main symptoms occur in three systems: skeletal, ocular, and cardiovascular [122]. It appears to be due to heterozygous mutation in the fibrillin-1 gene on chromosome 15q21. De Vries et al. [123] described Marfan syndrome in two cousins from a consanguineous Turkish family.

Inflammatory bowel diseases (IBD) in the form of Crohn disease and ulcerative colitis result from a dysregulated immune response to environmental factors in genetically susceptible people [124]. In a study, Crohn disease was found to be related with consanguinity [125].

Kindler syndrome, a rare subtype of inherited epidermolysis bullosa, shows oral symptoms such as gingivitis, periodontitis, and loss of teeth. Kindler syndrome is reported more frequently in populations with high rates of consanguinity [126].

5. Conclusion

There does not seem to exist sufficient research on periodontal diseases related to the genetic disorders. Moreover, further research is needed on periodontal diseases in relation to consanguineous marriages.

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